# Mediastinal Tumors of Thymic Origin

FREDERICK M. BINKLEY, M.D., JACK D. THORBURN, M.D.,
H. BRODIE STEPHENS, M.D., and ORVILLE F. GRIMES, M.D., *San Francisco*

*• Twenty-one cases of mediastinal tumors of thymic origin are presented. Five of these were benign and 16 malignant.*

*Surgical excision is proposed as the treatment of choice for the encapsulated benign tumors or for malignant tumors of limited extent. When surgical excision is not feasible, adequate roentgen therapy amounting to 5,000 to 6,000 r calculated tumor dose may eradicate or control the tumor.*

*No correlation between the histological pattern of the tumor and the survival rate or radiation response could be demonstrated in this small series.*

THE PROBLEM of thymic tumors has long been of great interest to clinicians and pathologists, no doubt owing to the incomplete knowledge about this gland. Many questions as to physiologic, pharmacologic, and pathologic factors lack conclusive answer. It is accepted that neoplasms of the thymus do occur and that the association of these tumors with myasthenia gravis is more than coincidental.[1, 5, 6, 10, 15] The majority of these tumors in patients having myasthenia gravis must be considered benign. It appears obvious that malignant thymic neoplasms occur not infrequently, but they are rarely associated with myasthenia.[9, 10, 11, 12, 13]

Seybold and associates[14] questioned the thymic origin of many of the previously reported malignant thymic tumors, as they found practically all tumors which they considered to be of thymic origin benign in character, both pathologically and clinically. However, the observations of the authors in 21 cases of such tumors were not in accord with those of Seybold and co-workers; in all cases sections were examined microscopically by numerous pathologists and all the neoplasms were considered to be of thymic origin. In no instance was there evidence suggesting that any of them could have been of bronchial origin or a teratoid tumor or a lymphoblastoma. In cases in which postmortem study was carried out, the impression gained at biopsy was confirmed.

## PATHOLOGY

Pathological classifications of thymic neoplasms have been numerous and inconsistent.[2, 3, 4, 8, 16] Classification has been further confused by doubt over the origin of the small round cells in the thymus, now generally accepted as being lymphocytes.[7, 8, 16] Lowenhaupt[7] recently introduced a classification based on the epithelial derivation of the neoplasm, pointing out that most thymic neoplasms duplicate cell types seen in the stages of embryological development of the thymus and that a close relationship exists between the various groups. No classification can be entirely satisfactory, for in the majority of tumors there are varying histological structures throughout the neoplasms, but usually one type of pattern will predominate.

Lowenhaupt's classification is as follows:

Group I. Carcinoma of primitive epithelial reticulum (Figure 1-A).
Group II. Carcinoma of variegated cell pattern (Figure 1-B).
Group III. Carcinoma of the granulomatous pattern (thymic Hodgkin's disease) (Figure 1-C).
Group IV. Carcinoma of thymic round cells (Figure 1-D).
Group V. Encapsulated thymoma (Figure 1-E).
Group VI. Carcinoma of the adamantinomatous pattern (Figure 1-F).

Lowenhaupt felt that all groups must be considered malignant with the exception of Group V, which is benign. It appears that the vast majority of tumors reported in association with myasthenia gravis have been of this latter type and have shown lymphocytic infiltration which suggests greater maturity.[7, 9, 10, 11, 12, 13]

In the present series the tumor was considered malignant in 16 of the 21 cases and they have been classified by Lowenhaupt as noted in Table 1. Four tumors were unclassified because of wide variation in cell pattern. In autopsy examinations, performed in seven cases, extensive local infiltration was observed consistently, with extension into the neck region most frequently, and less often infiltration below the diaphragm. Rarely was extension into the axilla observed. In no case in the series was dis-

From the Department of Surgery and Division of Thoracic Surgery, University of California School of Medicine, San Francisco.

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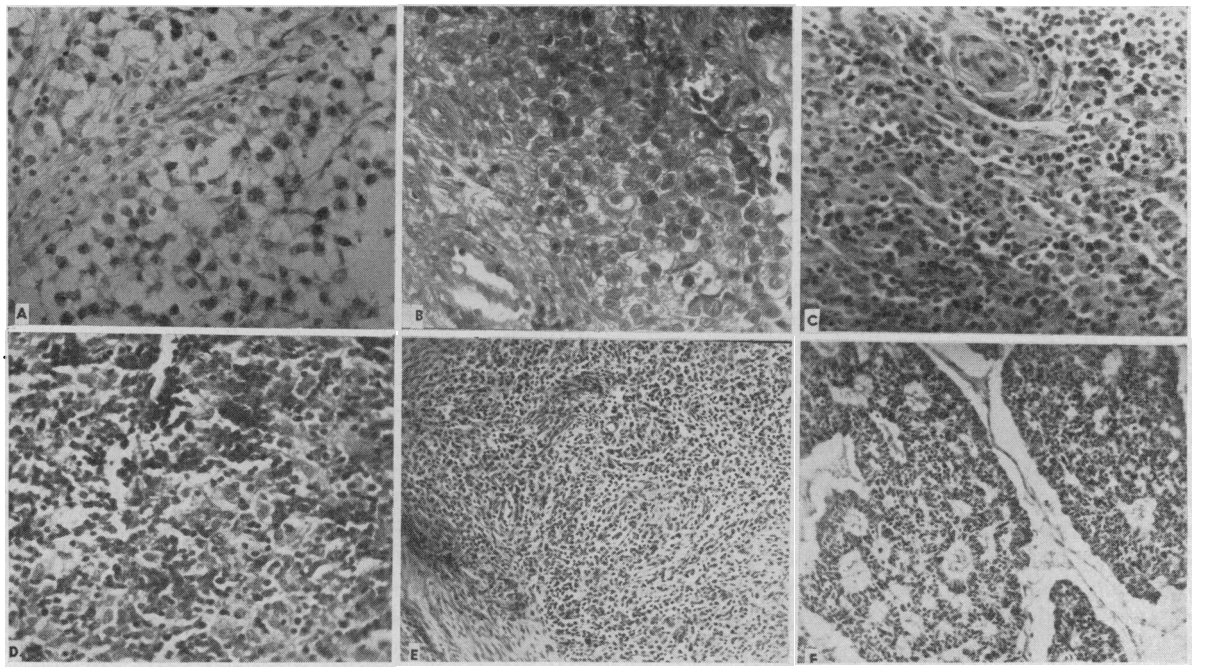

Figure 1.—*A*, Group I. Carcinoma of the primitive epithelial reticulum. This section, from the tumor in Case 1 (Table 1) shows the embryonal appearance and reticular nature of the cytoplasm of the tumor cells in this group.

*B*. Group II. Carcinoma of the variegated cell pattern. This section is from the same tumor as *A*, but shows the cell pattern seen in Group II. The fact that this picture came from a tumor which showed predominantly a reticular pattern indicates the close relationship of the various groups.

*C*. Group III. Carcinoma of the granulomatous pattern. This section, from Case 6, shows the lymphocytic and eosinophilic infiltration seen in this group of tumors.

*D*. Group IV. Carcinoma of the lympho-epitheliomatous pattern. This section, from Case 10, shows the lymphocytic infiltration and epithelial background of this group.

*E*. Group V. Encapsulated thymoma. Tumors of this group are seen most commonly in association with myasthenia gravis (Case 11).

*F*. Group VI. Carcinoma of the adamantinomatous pattern. It is felt that these cells spring directly from the primitive epithelial reticulum and that the pseudoglandular pattern can be explained by the close relationship of the anlage of the thymus to such neighboring organs as the parathyroids, salivary glands and enamel organs (Case 14).

tant metastasis noted, although such extension has been previously reported as an infrequent observation.[3, 8, 16]

### CLINICAL ANALYSIS

The present series comprises 21 proved thymic tumors seen at the University of California Hospital from 1925 to 1951, of which 16 were considered malignant and 5 benign. In all cases the diagnosis was made from pathological study of the excised neoplasm or of a biopsy specimen obtained at the operating table. Eight of the patients were between 20 and 30 years of age (Table 2), and only four were in or past the sixth decade. Sixteen patients were examined because of symptoms referable to a mediastinal tumor, but in five cases the presence of the tumor was observed radiologically in routine or survey chest films.

Two patients were considered to have myasthenia gravis in association with the tumor. A woman, 61 years of age, noted symptoms characteristic of myasthenia gravis for six months before admittance for study. A dose of 210 mg. of neostigmine bromide orally daily established satisfactory control. Following surgical excision of a thymoma in 1946, the patient was greatly improved and although she returned to strenuous farm labor she remained completely free of symptoms while taking a maintenance dose of 30 to 75 mg. of neostigmine bromide daily. Another woman, 58 years of age, had noted progressive loss of strength and diplopia for one year. Neostigmine was not given. A thymoma (Figure 2) was removed in 1945 and the patient had no further complaints. The diagnosis of myasthenia gravis in that case must be considered as presumptive. No other patients in the group had symptoms of sufficient magnitude to warrant a clinical diagnosis of myasthenia gravis.

Surgical excision was attempted in 14 of the 21 cases and in seven a biopsy specimen of the neoplasm was obtained. Four of the excised tumors were obviously incompletely removed and each of them was considered malignant. Five of the ten tu-

**TABLE 1.—*Clinical, Therapeutic and Pathologic Data on 21 Cases of Mediastinal Tumor of Thymic Origin.***

| Case | Age | Sex | Diagnosis | Group | Therapy | Follow-up | Autopsy Report | Remarks |
|---|---|---|---|---|---|---|---|---|
| 1* | 24 | M | Carcinoma | I | Radiation 3000 r | Died 9 years after therapy | No remaining tumor | Specimen obtained from biopsy |
| 2* | 50 | M | Carcinoma | I | Excision | Postoperative mortality | Local infiltration No metastases | Excision incomplete |
| 3* | 45 | M | Carcinoma | I | Radiation 1000 r | Died 3 months after therapy | No autopsy | Specimen obtained from biopsy |
| 4* | 42 | F | Carcinoma | I | Excision Radiation 2000 r | Died 1 year after therapy | No autopsy | Excision incomplete |
| 5* | 24 | M | Carcinoma | I | Excision Neutron ther. | Died 5 months after operation | No autopsy | Excision incomplete |
| 6* | 24 | M | Carcinoma | III | Radiation 5750 r | Alive 2 years after therapy | | No evidence of tumor |
| 7* | 28 | F | Carcinoma | III | Radiation 2500 r | Died 3 years after therapy | Extensive local infiltration. No distant metastases | Inadequate radiation due to erroneous initial diagnosis |
| 8* | 30 | F | Carcinoma | III | Excision Radiation 1 yr. later; 3050 r | Alive 2 years after radiation | | Secondary tumor in lung excised with primary tumor |
| 9* | 28 | F | Carcinoma | III | Excision Radiation 3120 r | Cervical recurrence, lt., 6 mo. rt. 9 mo.; radiation | | Alive. No evidence of recurrence 2 yrs. after radiation |
| 10* | 23 | M | Carcinoma | IV | Excision Radiation 3600 r | Recurrence 1 yr. after operation | Extensive local infiltration. No distant metastases | No tumor in areas irradiated at autopsy |
| 11* | 64 | F | Thymoma | V | Excision | Symptoms improved | | Clinical symptoms myasthenia gravis |
| 12 | 46 | F | Thymoma | V | Excision | Asymptomatic | | |
| 13* | 58 | F | Thymoma | V | Excision | Symptoms alleviated | | Symptoms suggested myasthenia gravis |
| 14* | 40 | M | Carcinoma | VI | Radiation 1945 3000 r Excision 1948 | Postoperative mortality | Local infiltration No metastases | No regression of tumor with radiation therapy |
| 15 | 63 | M | Carcinoma | VI | Excision Tumor adherent to pericardium | Died 3 months after operation | Local infiltration No metastases | History recurrent pericardial effusion 3 years |
| 16 | 63 | M | Carcinoma | VI | Biopsy | Postoperative mortality | Tumor adherent to superior vena cava and pericardium | |
| 17* | 45 | M | Carcinoma | VI | Excision | No recurrence in 5 years | | |
| 18 | 20 | F | Carcinoma | ? | Excision Radiation 5300 r | Asymptomatic 2 years after therapy | | No evidence of tumor |
| 19 | 33 | M | Carcinoma | ? | Radiation 2700 r | Died 2 months after therapy | No autopsy | Specimen obtained from biopsy |
| 20† | 37 | F | Chori-stoma | Be-nign? | Excision | Asymptomatic 1½ yrs. postop. | | Tumor located at interlobular septum |
| 21 | 33 | M | Cyst of thymus | Be-nign? | Excision | Asymptomatic 3 yrs. postop. | | |

* These cases previously reported by Lowenhaupt.[7]

† Case report to be published.

mors clinically completely excised were classified as benign. There were three postoperative deaths, two after incomplete excision of the tumor and one after excision of material for biopsy.

The majority of the operative procedures were done through a posterior lateral incision, which is the approach of choice especially for large tumors.

**TABLE 2.—*Age of Patients at Time of Study***

| Age | Total | Tumor | |
|---|---|---|---|
| | | Benign | Malignant |
| 20-30 | 8 | 0 | 8 |
| 31-40 | 3 | 2 | 1 |
| 41-50 | 6 | 1 | 5 |
| 51-60 | 1 | 1 | 0 |
| 61-70 | 3 | 1 | 2 |

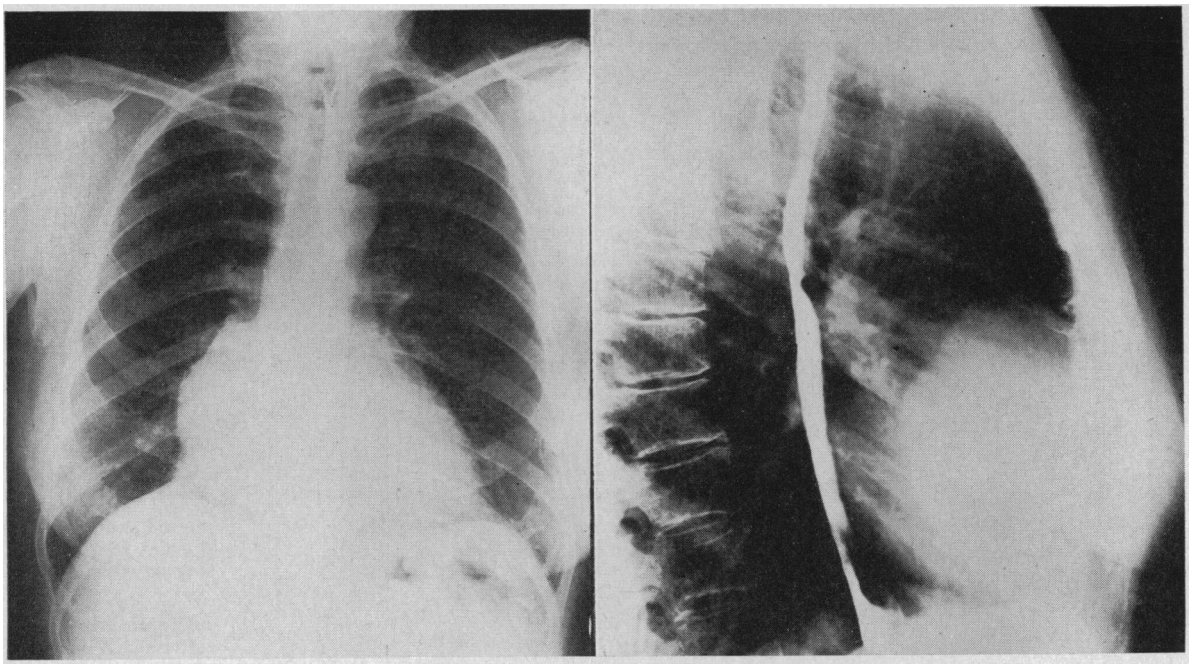

Figure 2.—Anterior mediastinal tumor best seen on the lateral projection (Case 13). Symptoms suggestive of myasthenia gravis were relieved by excision of the tumor which proved to be a benign thymoma.

The vertical or transverse sternal-splitting incision provides admirable exposure for all save the largest of tumors. In one instance a transverse sternal incision at the level of the nipples was combined with a necklace incision to expose the uppermost extension of the thymic tumor and the cosmetic result was excellent.

Roentgen therapy was given to 12 of the 16 patients with malignant thymic tumor. The pattern of therapy has varied considerably during the years of this study. In one case, neutron therapy consisting of 425 n through three separate fields was administered. Five patients received less than 3000 r calculated tumor dose in one series of treatments. In four cases 3000 to 3600 r was given over a period of 28 to 40 days. Recently the amount of radiation has been increased considerably and the last two patients treated by roentgen therapy were given a calculated tumor dose to the anterior mediastinum of 5300 r over a period of 38 days, and 5750 r in 48 days, respectively (Tables 3 and 4).

Of the 21 patients who were treated by operation or roentgen therapy, or both, ten were living, well and asymptomatic at the time of this report. Five of the ten were considered to have had benign tumors, three of them thymomas, one a thymic choristoma arising from a cell rest in the hilus of the left lung, and one a cyst containing thymic remnants in its wall. All of these benign tumors were completed excised, and the patients with thymomas had no evidence of recurrence five, six and eleven years after operation. The thymic cyst was removed three years ago and the choristoma in the past year.

The remaining five living patients had tumors that were classified as malignant. Three were classified as Group III by Lowenhaupt, one as Group VI, and one was unclassified because of the wide variation of cell pattern throughout. Three of the patients were operated upon for removal of the tumor, but excision was incomplete in one case and radiation therapy was given postoperatively. The two patients

**TABLE 3.—*Treatment of Malignant Tumors***

| | Living | Died | Total |
|---|---|---|---|
| Excision alone | 1 | 3* | 4 |
| Biopsy or excision plus x-ray <3000 r | | 6** | 6 |
| Biopsy or excision plus x-ray >3000 r | 4 | 2† | 6 |
| Total | 5 | 11 | 16 |

* Two died in postoperative period. ** One died in postoperative period. †No tumor found in treated area at autopsy.

**TABLE 4.—*Therapy of Malignant Tumors***

| | Alive | Dead |
|---|---|---|
| Complete surgical excision only | 1 | 1 |
| Clinically complete excision and roentgen therapy | 1 | 1 |
| Clinically incomplete excision and roentgen therapy | 1 | 2 |
| Biopsy and roentgen therapy | 2 | 4* |
| Operative mortalities | | 3 |

* In one case no tumor was observed at autopsy 9 years after therapy.

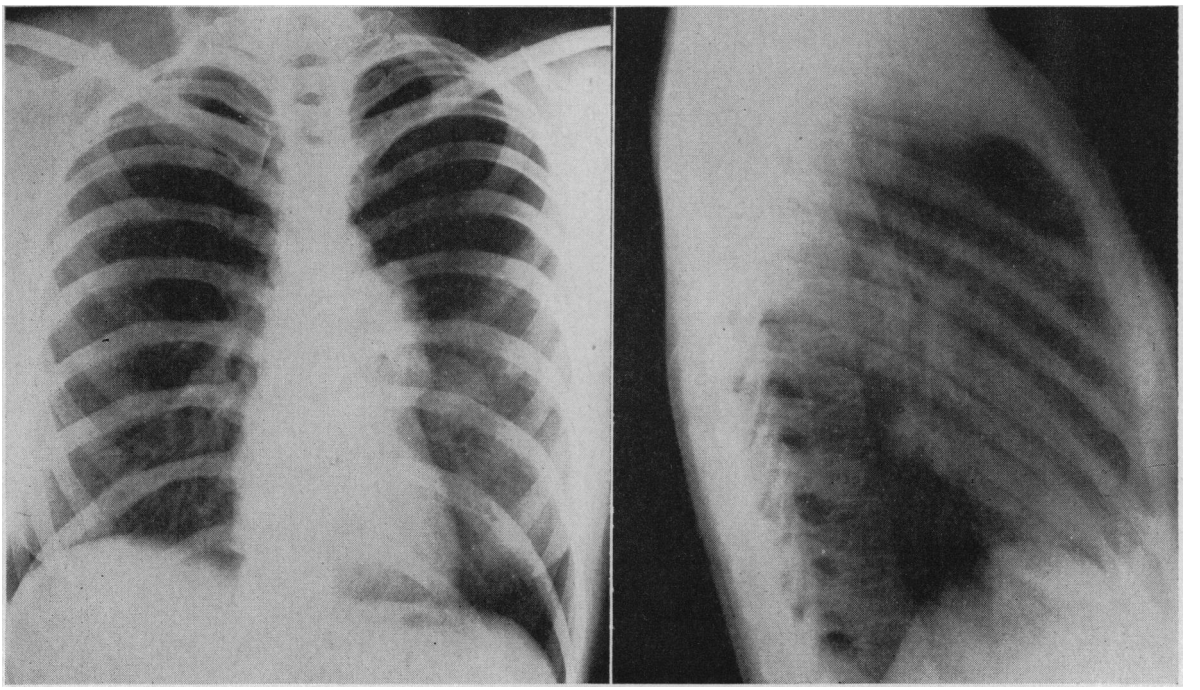

Figure 3.—Anteroposterior and lateral views of anterior mediastinal tumor which proved to be Group III (Case 8). A metastatic nodule in the left upper lobe not shown by x-ray was also excised at the time of removal of this tumor.

who were not operated upon had roentgen therapy after the nature of the tumor had been determined by biopsy.

One patient, a 30-year-old woman, had recurrence of tumor despite apparently complete excision. The seemingly encapsulated anterior mediastinal tumor (Figure 3) was relatively easily dissected free except for one area densely adherent to the pericardium which was excised with the tumor. In addition a circumscribed tumor 2 by 2 cm. in size in the upper portion of the left lower lobe was also resected. Both the primary and the metastatic nodule were considered malignant, but since they were grossly completely excised postoperative roentgen therapy was not given. A year later increased mediastinal density noted in an x-ray film of the chest was interpreted as a probable recurrence. Roentgen therapy was administered and the calculated mediastinal dose at the depth of the probable recurrence was 3020 r. At last report the patient had remained asymptomatic for two years after conclusion of therapy and no abnormality was observed in a film of the chest.

Complete excision of an apparently encapsulated tumor was readily accomplished in another patient, a 45-year-old man. The neoplasm was classified as a carcinoma of adamantinomatous pattern (Group VI). Postoperative radiation was not given. The patient remained asymptomatic and no evidence of recurrence was observed in a film of the chest more than five years after excision of the tumor.

Another of the three living patients with malignant tumors who were surgically treated, a 28-year-old woman, had a large anterior mediastinal tumor apparently arising in the right lobe of the thymus. The tumor was densely adherent to the innominate vein and vena cava and it was apparent that complete excision was not obtained. The left lobe of the thymus was identifiable in continuity with the tumor mass and was histologically normal, while the right lobe was replaced by tumor (Group III). Postoperative roentgen therapy was administered and the calculated tumor dose was 3120 r. Six months later a biopsy specimen was obtained from a left supraclavicular tumor mass which proved to be a recurrence of the thymic neoplasm. Roentgen therapy totalling 3922 r was given to this area and the mass disappeared. Three months later a small mass which appeared in the right supraclavicular area was also irradiated with a similar dose. This mass also disappeared and, at last report, two years after the last radiation therapy, the patient had no clinical evidence of recurrence.

One of the two living patients with malignant tumor who were not operated upon had a palpable mass in the left supraclavicular area at the time of admittance, in addition to a large mediastinal tumor visible in x-ray examination (Figure 4). After biopsy, roentgen therapy was administered. The calculated tumor dose in the mediastinum was 5750 r administered over 48 days and the dose to the left

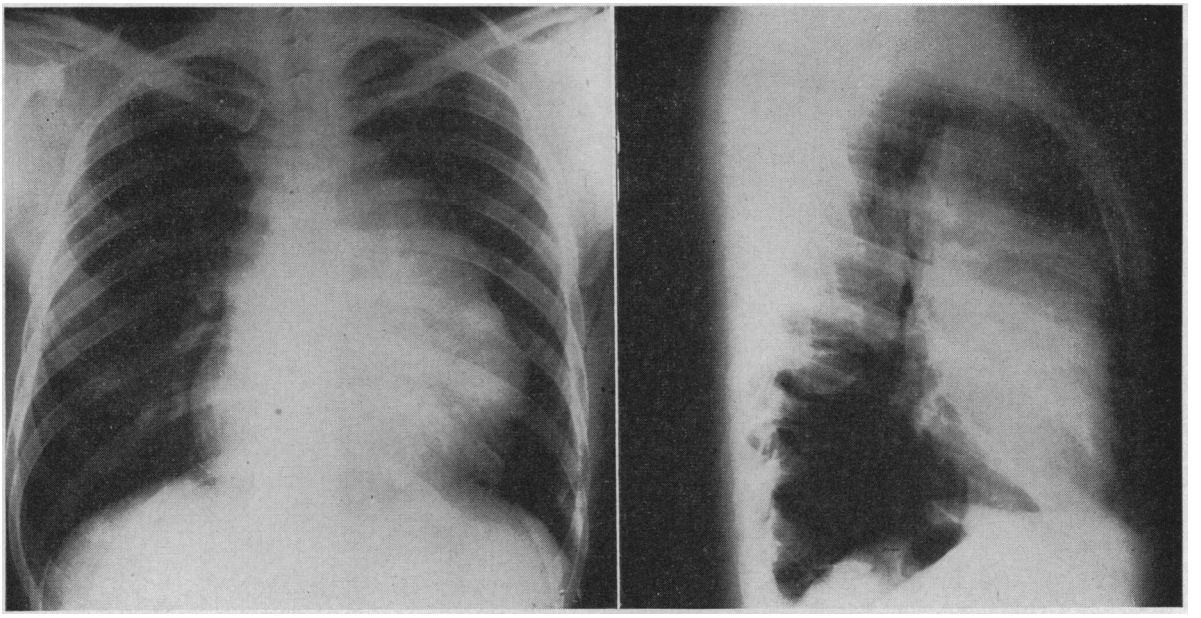

Figure 4.—Anteroposterior and lateral views of tumor classified as Group III (Case 6).

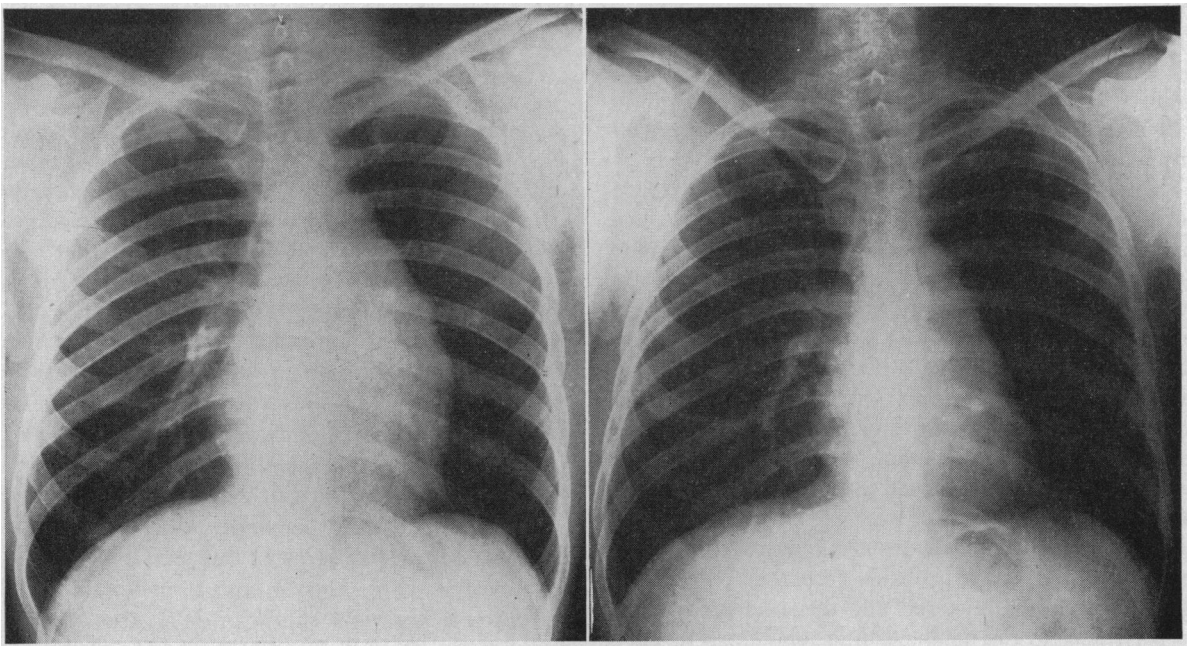

Figure 5.—Same patient as in Figure 4. *Left,* immediately after roentgen therapy of 5750 r calculated tumor dose. *Right,* complete disappearance of the tumor a year and a half later.

cervical area was 3000 r. The tumor rapidly regressed in size and at last report the patient had had no evidence of recurrence during the two years following completion of the radiation therapy (Figure 5).

The other of the two living patients with malignant growth who were not subjected to operation was a 20-year-old woman with a large anterior mediastinal tumor extending into the left supraclavicular fossa. By biopsy it was diagnosed as a thymic carcinoma, as yet unclassified. Roentgen therapy was given. The calculated tumor dose was 5300 r administered over 38 days. There was no evidence of tumor growth two years after completion of the therapy.

Eleven of the patients with malignant thymic tumors died, three of them in the postoperative period, as was previously mentioned. It is worthy of note

that one of the three (who had a Group VI tumor) received roentgen therapy amounting to 3000 r three years preoperatively and 1850 r again one year preoperatively without noticeable change in the rate of growth of the tumor. The patient died a few days after attempted excision of the tumor.

One patient (with Group I tumor) who was treated early in the series lived nine years after completion of roentgen therapy of approximately 3800 r. Postradiation fibrosis developed and it was complicated by bouts of massive hemoptysis. The patient died during exploratory thoracotomy done in hope of relieving the complication. At postmortem examination there was no evidence of residual tumor.

Another patient (with Group VI tumor) died three months after attempted excision of the tumor without receiving roentgen therapy. Two of the patients (one with Group I and the other with Group III tumor) who received over 3000 r died of extension of the disease, but at postmortem examination there was no evidence of tumor in the treated areas.

In four cases autopsy examination was not done. Three of the four patients received considerably less than 3000 r of roentgen therapy and one received neutron therapy as previously noted. In three of these cases the tumors were classified as Group I, and in the other the cell pattern was so variable as to be unclassifiable.

## DISCUSSION

In this limited series no correlation can be demonstrated between survival rates and pathological pattern of the tumor, nor can any conclusion be drawn as to optimum roentgen therapy for the various classes of tumors (Table 5). However, observations in these few cases suggest that the neoplasms are primarily locally invasive and that remote metastases occur infrequently. Therefore, early adequate operation would appear to offer hope of good results, such as were obtained in the case of the one patient with malignant disease in the present series who had adequate excision.

The postoperative deaths in this series should not discourage the surgical approach, for two of them occurred early in the series before the advent of antibiotics and present-day anesthesia, and in the third case the patient was already moribund from superior vena cava obstruction. The authors believe that all undiagnosed anterior mediastinal tumors warrant surgical exploration and, if resection is not feasible, a biopsy of the tumor to determine the advisability of roentgen therapy.

The four patients surviving two or more years after radiation therapy all had calculated tumor doses of more than 3000 r, and study of those cases and the two cases in which no tumor was observed in the

**TABLE 5.—*Results of Treatment of Malignant Tumors***

| Classification | Treatment | | | Results | |
|---|---|---|---|---|---|
| | Excision | Excision & X-Ray | Biopsy & X-Ray | Living | Died |
| I | 1* | 2 | 2 | 0 | 5 |
| III | | 2 | 2 | 3 | 1 |
| IV | | 1 | | | 1 |
| VI | 2* | 1 | 1* | 1 | 3 |
| Unclassified | | 1 | 1 | 1 | 1 |

* Postoperative death.

treated area at necropsy suggests that some of these tumors may be eradicable or controllable by roentgen therapy. In recent years 5000 to 6000 r has been administered over a period of 30 to 40 days with encouraging results.

As these neoplasms are not manifested by subjective complaints until they have reached a considerable size, diagnosis while they are in an early resectable stage will depend largely upon survey and routine x-ray examination of the chest. An unexplained mediastinal density should be viewed with a high degree of suspicion.

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